Once Versus Twice Daily Dose of Gentamicin Therapy in Thai Neonates

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Objective : *To compare the peak and trough gentamicin concentrations in neonates after a once (ODD) vs. twice daily dosing (TDD) to establish the appropriate dosage for Thai neonates.*
Material and Method : *Neonates of gestational age ≥ 34 weeks, or body weight ≥ 2000 g, suspected of having bacterial infection were randomized to receive gentamicin intravenously, either 5 mg/kg every 24 hours or 2.5 mg/kg every 12 hours. The peak and trough serum gentamicin levels (SGLs) were measured. Serum creatinine cued nephrotoxicity.*
Results : *Neonates were evaluated and baseline characteristics between the groups were compared. The ODD and TDD group had a mean gentamicin peak and trough concentration of 10.1 ± 3.0 vs. 7.8 ± 2.0 μg/ml ($p < 0.05$) and 1.6 ± 1.1 vs. 2.6 ± 1.2 μg/ml ($p < 0.05$), respectively. The peak SGL of ≥ 4 μg/ml was achieved in 100% vs. 96% of the ODD vs. TDD group, respectively. SGL troughs ≥ 2 μg/ml were detected less often in the ODD group (22% vs. 68%; $p < 0.05$). Abnormal change in serum creatinine was not observed in either group.*
Conclusion : *A once dialy dose of gentamicin 5 mg/kg achieved a significantly higher peak SGL and safer trough than a twice-daily dose of 2.5 mg/kg albeit about a quarter of the ODD group had high troughs. A single daily dose of gentamicin 3.5-4 mg/kg/d in Thai neonates should be tested.*

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Gentamicin and ampicillin are widely used as empirical therapy for neonates with suspected sepsis[1-4]. Advances in antibacterial mechanisms and the pharmacodynamics of aminoglycosides have necessitated a reassessment of dosing because: 1) the concentration-dependent bactericidal effect of aminoglycosides needs a high peak concentration to kill more bacteria[5]; 2) the post-antibiotic effect is also concentration-dependent[6,7]; and 3) adaptive resistance by the bacteria may occur after continuous exposure to drug concentrations below the minimal inhibitory level[7,8]. Importantly, neonates have a large volume of distribution and slow renal clearance of aminoglycosides[9,10]. Based on these factors, a high dose at long intervals would suit neonates. Studies in adults indicate a single daily dose maximized bactericidal activity and might, therefore, minimize the recognized toxicity of gentamicin[7,11-13]. Less is known about a once daily administration of aminoglycosides in neonates though some neonatal references suggest varying dose schedules for neonates[1,2,4].

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Objective

To investigate the appropriate gentamicin dose for Thai neonates ≥ 2,000 g.

Material and Method

The present study was a randomized, controlled trial conducted between May 2000 and August 2001 in the Neonatal Care Unit at Srinagarind Hospital, Khon Kaen University, Northeast Thailand. The decision to initiate gentamicin therapy was made by the attending neonatologist. Included were neonates: 1) ≥ 2,000 g; 2) between 0 and 7 days old; 3) with an APGAR score > 6 at 5 minutes; and suspected

of having sepsis. Excluded were those with a history of: 1) perinatal asphyxia; 2) shock; 3) cardiopulmonary arrest; 4) seizure or neuromuscular disorder; or 5) anomalies of the kidney or ear.

The Ethics Review Committee of the university approved the protocols and written consent was obtained from the legal guardians.

Neonates were assigned to either the once daily dose (ODD) or twice daily dose (TDD) group from a computer-generated, randomized list kept in a sealed envelope. The ODD group was given gentamicin 5 mg/kg every 24 hours and the TDD group (the control) 2.5 mg/kg every 12 hours.

Gentamicin doses were diluted to 1-5 mg/ml and infused over 60 minutes with a metered syringe pump and microbore tube. The peak serum gentamicin level (SGL) was measured 30 minutes after infusion (after the third dose in the ODD group and the sixth dose in the TDD group). SGL troughs were measured immediately before the fourth dose in the ODD group and the seventh dose in the TDD group. Serum gentamicin was measured by fluorescent polarization immunoassay (Abbott TDX/FLX; Abbott Park; Illinois). The results, were then used to calculate the pharmacokinetic parameters of each individual patient by using the steady-state Sawchuck-Zaske method[14]. Serum creatinine was measured on days 0, 3 and 7 or the discontinuation day.

Statistical analysis

The authors compared the between-group SGL peaks and troughs using the unpaired student's *t* test. A chi-square analysis was used to compare the control and study groups for the frequency of SGL in the desired range. A p value < 0.05 indicated statistical significance. Data are expressed as the mean $\pm$ S.D.

Results

Patients

Sixty-four neonates were evaluated: 33 and 31 in the ODD and TDD groups, respectively. Baseline characteristics before enrollment were comparable (Table 1). Birth weights in the ODD and TDD groups averaged 3,044 g (range, 2,300 to 3,890) and 3,036 g (range, 2,050 to 3,770), respectively. Most of the infants had a gestational age $\geq$ 37 weeks, except 2 and 3 infants in the ODD and TDD groups, respectively. Between the two groups, mean weight, gestational age and maternal conditions were not significantly different. Respiratory distress and suspected sepsis were the common clinical diagnoses (Table 2).

Table 1. Baseline characteristics of neonates in the ODD and the TDD groups

Baseline data	ODD (N = 33)	TDD (N = 31)
Gestational age at birth (wk)		
Mean SD	38.4(1.8)	38.6(2.1)
Range	34-42	34-43
$\geq$ 37 wks (%)	31(94)	28(90)
34-36 wks (%)	2(6)	3(10)
Birth weight (g)		
Mean SD	3,044(475)	3,036(497)
Range	2,300-3,890	2,050-3,770
< 2,500	5	4
Maternal PROM*	4	4
Maternal antibiotic	2	-

* PROM = premature rupture of membrane >24 hours

Table 2. Initial diagnoses of 64 neonates before starting empirical gentamicin

Clinical manifestations	ODD N=33	BID N=31
Respiratory distress	15	15
- Presumed pneumonia	8	5
- Pneumothorax	2	-
- Idiopathic respiratory distress syndrome	1	3
- Meconium aspiration syndrome	2	3
- Others	2	4
Necrotizing enterocolitis	1	2
Suspected, undefined sepsis	17	14

Table 3. Comparison of peak and trough serum gentamicin concentrations in the ODD vs. TDD groups

	OD N=33	TDD N=31
Peak (μg/ml)		
Mean SD	10.1 3.0	7.8 2.0*
Range	4.1-16.2	2.7-11.9
Number of SGC <4 μg/ml (%)	0(0)	1(4)
Number of SGC >12 μg/ml (%)	7(21)	0(0)*
Trough (mg/ml)		
Mean SD	1.6 1.1	2.6 1.2*
Range	0.6-4.7	0.3-5.3
Number of SGC >2 μg/ml (%)	8(22)	21(68)*

* $p < 0.05$

Pharmacokinetics

Gentamicin was started in all the neonates before seven days of age. The pharmacokinetic data for both groups are presented in Table 3. The mean

peak SGL was significantly higher in the ODD group (10.1 ± 3.0 μg/ml) than that of the TDD group (7.8 ± 2.0 μg/ml). All the neonates on the ODD regimen had SGL peaks > 4 μg/ml and seven (21%) had peaks > 12 μg/ml (range, 12.8 to 16.2 μg/ml). The only child with a sub-therapeutic peak was a term infant in the TDD group.

The mean SGL trough was significantly lower in the ODD group. Of the 64 neonates, 22 and 68 percent in the ODD and TDD groups, respectively, had serum gentamicin troughs > 2 μg/ml. Two neonates in the ODD group were exposed to gentamicin antenatally as their mothers were treated for a urinary tract infection. Each of these neonates had a SGL peak of 7.4 and 5.4 μg/ml and a SGL trough of 1.2 and 0.8 μg/ml, respectively.

The means of the volume of distribution, elimination half-life and elimination constant were 0.5 ± 0.2 l/kg, 8.3 ± 2.7 hours and 0.09 ± 0.02, respectively.

Renal

Serum creatinine changed non-significantly between days 3 and 8, and no oliguric or polyuric problems occurred during therapy. The mean serum creatinine at baseline and on the discontinuation day was 0.8 ± 0.3 mg/dl and 0.5 ± 0.2 mg/dl in both groups, respectively. Most of the neonates received combined antibiotic therapy that included penicillin or ampicillin (Table 4). Two neonates in each group received cloxacillin. Only one child in the ODD group, whose mother had premature membrane rupture, developed group B streptococcal bacteremia. Hemoculture was negative for the other neonates.

The authors evaluated the clinical response using an inclusion point of 'improvement within 72 hours of treatment'; whereas, excluded from the clinical evaluation were neonates with metabolic disturbance, congenital heart disease or gram-positive bacterial infection. There were two gram-positive bacterial infections, one with a group B streptococcal septicemia in the ODD group and one with a group D streptococcal infection in the TDD group. The clinical response between groups was not significantly different (Table 4). Of the two neonates in the TDD group, who did not respond to therapy, one was diagnosed with bacterial meningitis and the antibiotic was changed to cefotaxime. The other neonate, who was treated with cloxacillin and gentamicin, had a nosocomial infection after five days of therapy. The blood and cerebrospinal fluid cultures for both patients were negative.

Table 4. Comparison of concomitant antibiotics and clinical response between the two groups

	ODD N=33	TDD N=31
Concomitant antibiotic		
Penicillin	16	10
Ampicillin	15	19
Cloxacillin	2	2
Clinical response(%)	24/24(100)	25/27(93)

Discussion

In the present study, the measured SGL peak in the ODD group ranged between 4.1 and 16.2 μg/ml (mean 10.0 ± 3.0 μg/ml), which was significantly higher than the TDD group (7.8 ± 2.0 μg/ml). This mean SGL peak level was consistent with previous reports using gentamicin 5 mg/kg/ODD[15-17] but higher than a similar Thai study[18]. Twenty-one percent of the neonates in the ODD group had SGL peaks > 12 μg/ml, which represents a higher proportion than found in other reports[15,17-19], perhaps because of a lower volume of distribution. Most studies achieved appropriate SGL troughs (< 2 μg/ml) at this dosage, whereas 22% of the neonates in the ODD group had high SGL troughs, suggesting slower renal clearance.

Thirty of the 31 neonates in the TDD group achieved the target SGL peak; however, a high percentage (68%) of inappropriate SGL troughs persisted, confirming a slow renal clearance in the neonates. In general, TDD administrations had more inappropriate SGL troughs (> 1.5-2 μg/ml) than the ODD regimen[15-17,20]. With a high percentage of SGL troughs > 2 μg/ml in the present study, 5 mg/kg/day of TDD gentamicin might not be appropriate for neonates in Northeast Thailand.

Several studies in adult patients with pneumonia and sepsis revealed that the clinical response to aminoglycosides, such as gentamicin, depends on the peak serum concentrations and the peak-to-MIC ratio[21,22]. Antibiotic therapy in most neonates is started on an empirical basis as it was in the present study and others[15-20]; therefore, a SGL peak > 12 μg/ml is not needed and the SGL trough should be kept below 2 μg/ml. In the present study, the ODD regimen of gentamicin 5 mg/kg/day achieved better SGL troughs than the TDD regimen but 22% still had high troughs (> 2 μg/ml) and 21% had high peaks (> 12 μg/ml). The average volume of distribution (Vd) in the neonates was 0.5 ± 0.2 l/kg and the elimination half-

life ($T_{1/2}$) was 8.3 ± 2.7 hours. From these pharmacokinetic para-meters, the predicted peak and trough SGL would be 8.3 and 1.0 μg/ml for 30-minute ODD administration of gentamicin 4 mg/kg/day. Studies using an ODD of gentamicin 4 mg/kg/day in neonates achieved appropriate peaks and troughs[6,20,23-25]. A study of 4 mg/kg/day ODD in neonates > 2,000 g is underway at the authors' hospital.

Nephrotoxicity usually occurs 7 to 10 days after therapy[26]. Most neonatal gentamicin therapies including the present study, are brief (i.e. 3 to 7 days) and therefore safe[15-20]. There was no nephrotoxicity detected in either group of the neonates. Ototoxicity associated with aminoglycoside therapy is rare and reported in only two studies[8,27]. The authors did not assess ototoxicity in our infants.

Conclusion

The pharmacokinetic parameters of gentamicin used in neonates in Northeast Thailand revealed that 2.5 mg/kg TDD could not achieve a safe SGL trough and 5 mg/kg ODD had inappropriately high peaks and some deep troughs. There was no evidence of renal toxicity in either of the treatment groups. The authors suggest 3.5 to 4.0 mg gentamicin/kg ODD as the most appropriate dosage for neonates.

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การศึกษาเปรียบเทียบการให้ยา Gentamicin แบบวันละครั้งกับการแบ่งให้วันละสองครั้งในทารกแรกเกิด

ภพ โกศลารักษ์, ผกามาศ จันทร์เทพ, จรรยา จิระประดิษฐา, สุกัญญา ทักษพันธุ์, ผกาพรรณ เกียรติชูสกุล

วัตถุประสงค์ *: ศึกษาระดับยาสูงสุดและต่ำสุดในเลือด โดยการให้ยา Gentamicin แบบวันละครั้งกับการแบ่งให้วันละสองครั้งในทารกแรกเกิด เพื่อหาขนาด และวิธีการบริหารยาให้ได้ระดับยาที่เหมาะสม*

รูปแบบการวิจัย *: ศึกษาทารกแรกเกิดที่มีอายุครรภ์มากกว่า 34 สัปดาห์ หรือน้ำหนักตัวมากกว่า 2,000 กรัม ในโรงพยาบาลศรีนครินทร์ซึ่งมีอาการ และอาการแสดงที่สงสัยภาวะติดเชื้อ และได้รับยา Gentamicin โดยแบ่งทารกเป็นสองกลุ่มด้วยวิธีสุ่มกลุ่มควบคุมจะได้รับยา Gentamicin 2.5 มก./กก./ครั้ง ทุก 12 ชั่วโมงทางหลอดเลือดดำ ส่วนกลุ่มทดลองจะได้รับยา Gentamicin 5 มก./กก./ครั้ง ทุก 24 ชั่วโมง ตรวจวัดระดับยาสูงสุด และต่ำสุด และประเมินภาวะพิษต่อไตโดยใช้การเปลี่ยนแปลงของค่า creatinine ในเลือด*

ผลการศึกษา *: ทารกที่ศึกษา 64 รายเป็นกลุ่มที่ได้รับยา Gentamicin วันละครั้งจำนวน 33 ราย และเป็นกลุ่มที่ได้รับยาแบบแบ่งให้วันละสองครั้งจำนวน 31 ราย ข้อมูลพื้นฐาน อาการ อาการแสดง และยาต้านจุลชีพที่ใช้ร่วมระหว่างกลุ่มไม่มีความแตกต่างกัน การตรวจระดับยาในเลือดพบว่ากลุ่มที่ได้รับยาวันละครั้งมีระดับยาสูงสุดในเลือดสูงกว่า (10.1 ± 3.0 และ 7.8 ± 2.0 ไมโครกรัม/มล.) และมีระดับยาต่ำสุดในเลือดต่ำกว่า (1.6 ± 1.1 และ 2.6 ± 1.2 ไมโครกรัม/มล.) กลุ่มที่ได้รับยาแบบแบ่งให้วันละสองครั้งอย่างมีนัยสำคัญทางสถิติ ทารกกลุ่มที่ได้รับยาวันละครั้งมีระดับยาต่ำสุดที่ไม่เหมาะสม (> 2.0 ไมโครกรัม/มล.) น้อยกว่ากลุ่มที่ได้รับยาแบบแบ่งให้วันละสองครั้งอย่างมีนัยสำคัญทางสถิติ อย่างไรก็ตามไม่มีทารกมีค่า creatinine ในเลือดผิดปกติจากการบริหารยาทั้งสองแบบ*

สรุป *: การให้ยา Gentamicin ขนาด 5 มก./กก.ทุก 24 ชั่วโมง ให้ระดับยาสูงสุดในเลือดสูงกว่า และให้ระดับยาต่ำสุดในเลือด ในเกณฑ์ที่เหมาะสมมากกว่าการแบ่งให้วันละสองครั้ง อย่างไรก็ตามประมาณหนึ่งในสี่ของทารกที่ได้รับยาแบบแบ่งให้วันละครั้ง ยังมีระดับยาต่ำสุดในเลือดอยู่ในเกณฑ์ที่ไม่เหมาะสม การให้ยา Gentamicin ขนาด 3.5-4 มก./กก.ทุก24 ชั่วโมงน่าจะให้ระดับยาในเลือดที่เหมาะสมกว่า และควรมีการศึกษาต่อไป*